PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Rec'd PCT/PTO 25 MAR 2005

PCT

To: FC

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REPLY TO:
WRITTEN OPINION
(PCT Rule 66)

NOV
DUE ON 05 2004

Date of mailing *(day/month/year)*	05.07.2004
Applicant's or agent's file reference: 14226-12PCT	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA 03/01477	25.09.2003	26.09.2002

International Patent Classification (IPC) or both national classification and IPC
C12N15/12

Applicant
CENTRE FOR TRANSLATIONAL RESEARCH IN CANCER et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 26.01.2005

Name and mailing address of the international preliminary examining authority:

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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-39 as originally filed

Claims, Numbers

1-42 as originally filed

Drawings, Sheets

1/12-12/12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☒ furnished subsequently to this Authority in written form.
   ☒ furnished subsequently to this Authority in computer readable form.
   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☐ claims Nos.

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 24-38

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-4 , 12 17-19 25-28 30-35 37
Inventive step (IS)	Claims	1-4 , 9,10,12,17-19,25-43
Industrial applicability (IA)	Claims	

2. Citations and explanations

   see separate sheet

Reference is made to the following documents:

D1: VO N ET AL: "Acetylation of nuclear hormone receptor-interacting protein RIP140 regulates binding of the transcriptional corepressor CtBP." MOLECULAR AND CELLULAR BIOLOGY. UNITED STATES SEP 2001, vol. 21, no. 18, September 2001 (2001-09), pages 6181-6188, XP002269408 ISSN: 0270-7306

D2: HÖRLEIN A J ET AL: "Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor co-repressor." NATURE. ENGLAND 5 OCT 1995, vol. 377, no. 6548, 5 October 1995 (1995-10-05), pages 397-404, XP002269409 ISSN: 0028-0836

D3: DATABASE TREMBL [Online] 1 December 2001 (2001-12-01), NAGASE,T. ET AL.: "Hypothetical protein KIAA1795 (Fragment)" XP002269412 retrieved from EBI Database accession no. Q96JN0

The present application relates to the LCoR transcriptional corepressor , having the molecular sequence data with seq.1,2 , that is binding to the nuclear receptor estrogen receptor through a single LXXLL motif at positions 53-57
and is binding to the C-terminal binding protein corepressors CTBP through the motifs PLDLDLTVR at positions 64-70 and VLDLSTK at positions 82-88 .
A mutant disrupted in the LXXLL shows a disrupted hormone dependent interaction .

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 24-38 relate to subject-matter considered by this Authority to be covered by the provisi-ons of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the present claims 24-38 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Novelty(Article 33.2 PCT)

D1 discloses that CtBP (carboxyl-terminal binding protein) participates in regulating cellular development and differentiation by associating with a diverse array of *transcriptional repressors*. Most of these interactions occur through a consensus CtBP-binding motif, PXDLS, in the repressor proteins. CtBP was shown to interact with co- repressor RIP140 in vitro and in vivo through a sequence, PIDLSCK, in the amino-terminal third of the RIP140 protein . RIP140 contains nine *LXXLL motifs* . Yeast two-hybrid CtBP interaction assays identified the binding motifs *pldltvr* and *vldlstk* from unknown proteins . It discloses that Myt1 and RIZ contain two CtBP-binding motifs . The unacetylated nuclear hormone receptor-interacting protein RIP140 acts as a transcriptional repressor through its interaction with CtBP . RIP140 represses nuclear hormone receptor-dependent transcription, via the estrogen recpetor. (see the abstract, table 1 , page 6186 left hand column second paragraph and page 6187 right hand column second paragraph)

D2 discloses the nuclear receptor co-repressor NCoR comprising LXXLL at amino acid positions 674-678 . The transcription coprepression acts via the Receptors of Retinoic Acid or Thyroid Hormone (see the abstract and figure 2)

In view of D1-D2 , the subject matter of claims 1-4,12,17-19 , 25-28, 30-35 ,37 covering nuclear receptor co-repressor having LXXLL is not new .

2. Inventive step(Article 33.3 PCT)

2.1 Subject-matter concerning claims 9,10 and 29,36,38-43

D1 is considered to be the closest prior art .

The subject matter of claims 9,10 differs from D1 by the presence of both *pldltvr* and *vldlstk* motifs binding to CtBp , instead of the PIDLSCK, in the amino-terminal third of the RIP140 protein , and differs from the subject mater of claims 29,36,38-43 by the provision of a method of assaying binding modulators.

The first problem to be solved is the provision of nuclear receptor transcriptional corepressors possessing alternative CtBP binding motifs and the second problem to be solved is the provision of further binding modulations .

The person skilled in the would have had the incentive to solve both problems in view of the therapeutical importances of nuclear receptor transcriptional corepressors .

In view of D1 disclosing explicitely that both *pldltvr* and *vldlstk* are binding motifs to CtBp, in view of D1 disclosing that CtBP is associated with a diverse array of transcriptional repressors through the consensensus bindin motif PXDLS , in view of D1 disclosing explicitely that the motif PXDLS is inlcuding *pldltvr* and *vldlstk*, and in view of D1 disclosing that CtBP-binding proteins can contain two PXDLS motifs , the person skilled in the art , with his knowledge of the field would had reasonable expectation of providing a furhter nuclear receptor transcriptional corepressors possessing *both pldltvr and vldlstk CtBP binding motifs* .
Moreover , as a standard practice he would have modified the methods of modualtion a cell and the binding assay disclosed in D1 , to regulate gene expression test the binding activtiy of potenital modulators of binding implicated in hormone nuclear receptor dependent cancers . Hence , the subject matter of claims 9,10 and 29,36,38-43 lack an inventive step .

2.2 Subject-matter concerning claims 5-8,11,13,16,22,23,24

D3 discloses the Hypothetical protein KIAA1795 showing 100.000% identity (100.000% ungapped) in 433 aa overlap (1-433:140-572) with seq.2 of the present application . It contains a DNA binding , a regulation of transcription, DNA-dependent and a Homeodomain_like domain , however it *was not annotated as a transcription repressor and fails to comprise the LXXL , pldltvr and vldlstk motifs* (see the whole document)

D1 is considered to be the closest prior art .

The subject matter of claims 5-8 ,11, 13, 16, 22 ,23,24 differs from D1 by the provision of the molecular sequence date from fig.1D of the present application .
The problem to be solved is the provision of a nuclear receptor transcriptional with an alternative overall molecular data sequence .

The person skilled in the art would have had the incentive to solve this problem in view of the therapeutical importances of nuclear receptor transcriptional corepressors .

While the prior art is not suggesting any homologous sequence to fig1d possessing LXXL , pldltvr and vldlstk motifs and is not suggessting that any homologous sequence to fig1d would act as transcriptional repressor , the person skilled in the art would have NO reasonable expectation of succes of cloning the nuclear receptor transcriptional corepressor with the molecular sequence data of fig.1d of the present application . The subject matter of claims 5-8 ,11, 13, 16, 22-24 is hence inventive .